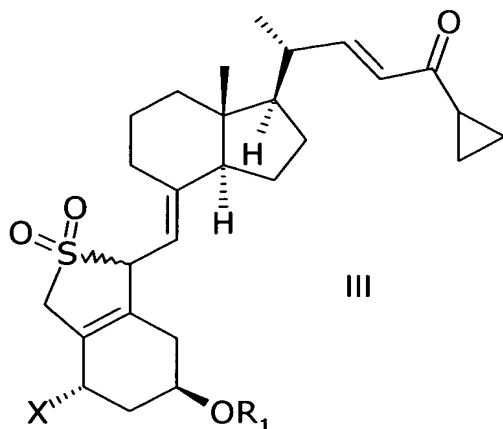
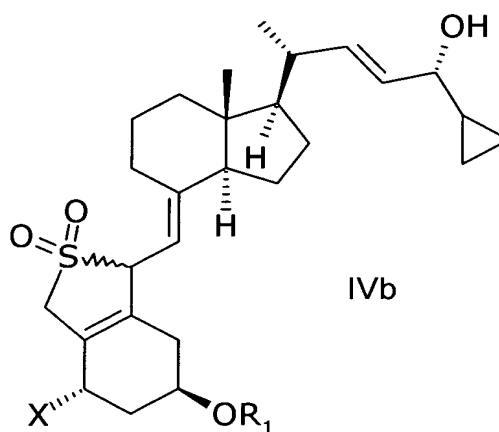
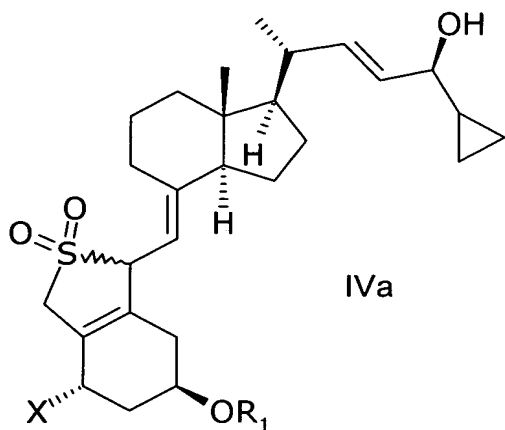


## CLAIMS

1. A method of reducing a compound of general structure III,

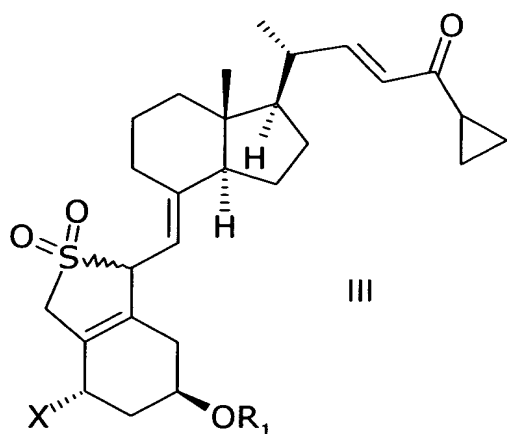


- 5 wherein X represents either hydrogen or  $\text{OR}_2$ ,  
 and wherein  $\text{R}_1$  and  $\text{R}_2$  may be the same or different and represent hydrogen, or a  
 hydroxy protecting group,  
 in an inert solvent with a reducing agent or with a reducing agent in the presence of a  
 chiral auxiliary,  
 10 to give a mixture of compounds of general structure IVa and IVb,



which is enriched with IVa, wherein X,  $\text{R}_1$ , and  $\text{R}_2$  are as defined above.

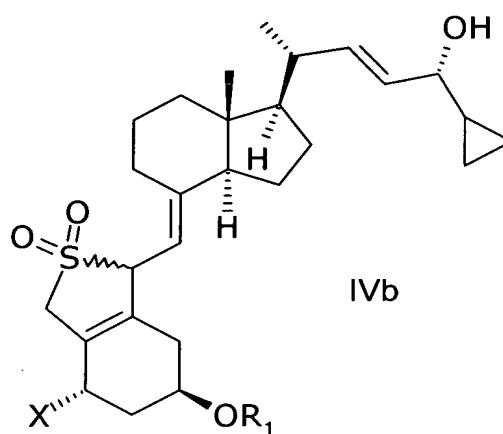
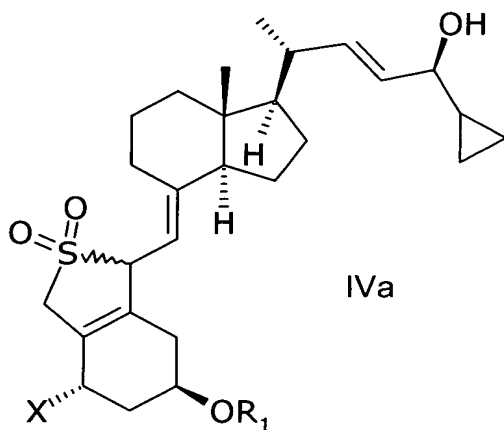
- 15 2. A method for producing calcipotriol {(5Z, 7E, 22E, 24S)-24-cyclopropyl-9,10-  
 secochole-5,7,10(19),22-tetraene-1 $\alpha$ -3 $\beta$ -24-triol} or calcipotriol monohydrate  
 comprising the steps of:  
 (a) reducing a compound of general structure III,



wherein X represents  $OR_2$ ,

and wherein  $R_1$  and  $R_2$  may be the same or different and represent hydrogen or a hydroxy protecting group,

- 5 in an inert solvent with a reducing agent or with a reducing agent in the presence of a chiral auxiliary,  
to give a mixture of compounds of general structure IVa and IVb,  
which is enriched with IVa,

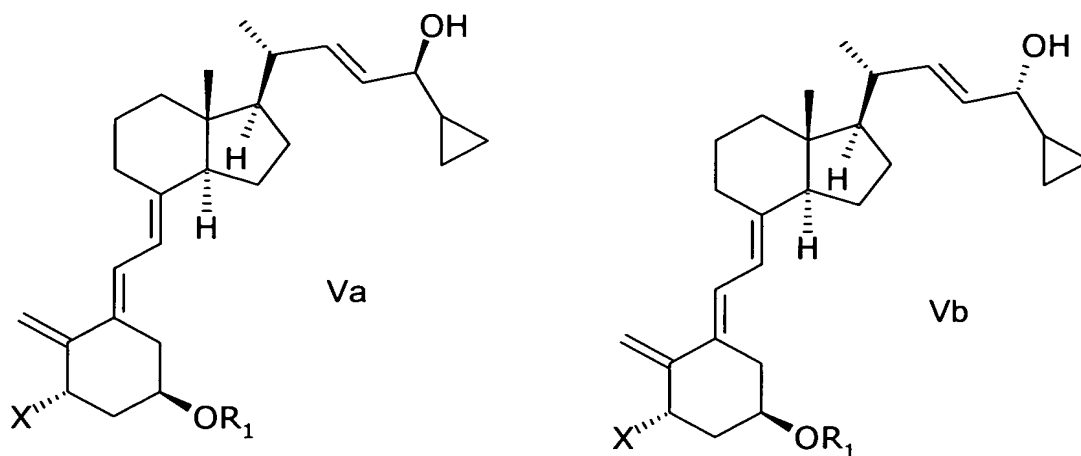


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wherein X,  $R_1$  and  $R_2$  are as defined above;

(b) reacting the mixture of compounds of general structure IVa and IVb, which is enriched with IVa, in the presence of a base to give a mixture of compounds of general

structure Va and Vb, which is enriched with Va,

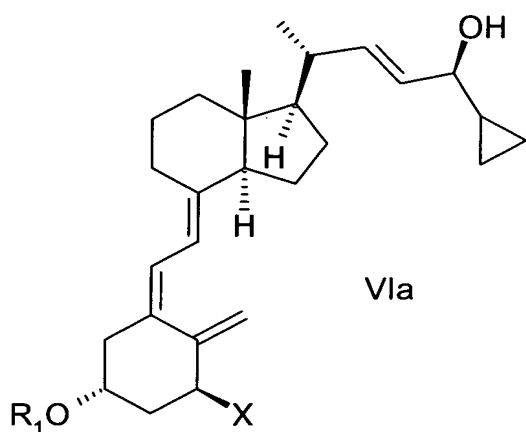


wherein X, R<sub>1</sub> and R<sub>2</sub> are as defined above;

- 5 (c) separating the compound of general structure Va from the mixture of compounds of general structure Va and Vb which is enriched with Va, wherein X, R<sub>1</sub> and R<sub>2</sub> are as defined above;

(d) isomerising the compound of general structure Va to the compound of general structure VIa,

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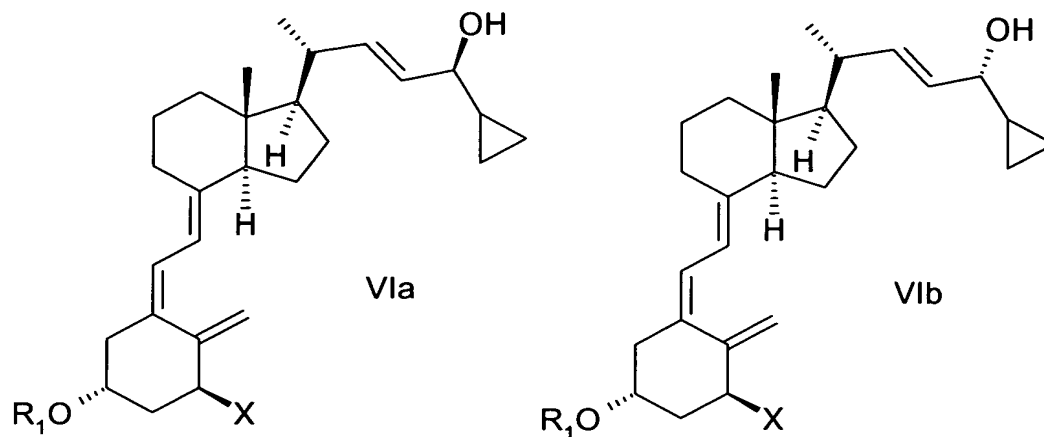


wherein X, R<sub>1</sub> and R<sub>2</sub> are as defined above; and

- (e) when R<sub>1</sub> and/or R<sub>2</sub> are not hydrogen, removing the hydroxy protecting group(s) R<sub>1</sub> and/or R<sub>2</sub> of the compound of general structure VIa to generate calcipotriol or calcipotriol monohydrate.
- 15

3. A method for producing calcipotriol or calcipotriol monohydrate comprising steps (a) – (b) of claim 2 and further comprising the steps of:

(f) isomerising the mixture of compounds of general structure Va and Vb, wherein X, R<sub>1</sub> and R<sub>2</sub> are as defined in claim 2, which is enriched with Va, to a mixture of compounds of general structure VIa and VIb, which is enriched with VIa,



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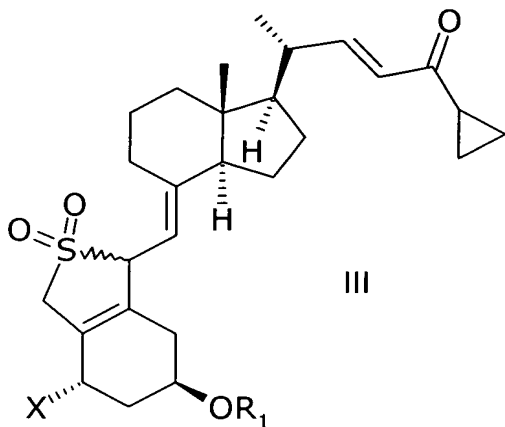
wherein X, R<sub>1</sub> and R<sub>2</sub> are as defined above;

(g) separating the compound of general structure VIa from the mixture of compounds of general structure VIa and VIb which is enriched with VIa, wherein X, R<sub>1</sub> and R<sub>2</sub> are as defined above;

10 (h) when R<sub>1</sub> and/or R<sub>2</sub> are not hydrogen, removing the hydroxy protecting group(s) R<sub>1</sub> and/or R<sub>2</sub> of the compound of general structure VIa to generate calcipotriol or calcipotriol monohydrate.

4. A method for producing calcipotriol {(5Z, 7E, 22E, 24S)-24-cyclopropyl-9,10-secochole-5,7,10(19),22-tetraene-1α-3β-24-triol} or calcipotriol monohydrate  
15 comprising the steps of:

(j) reducing a compound of general structure III,

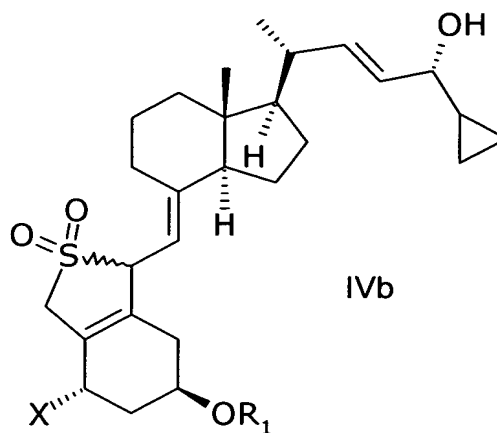
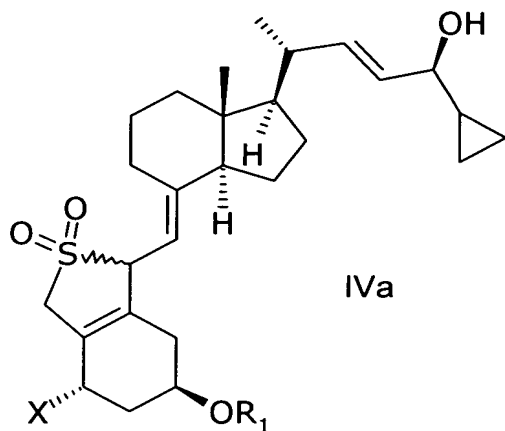


wherein X represents hydrogen,

and wherein  $R_1$  represents hydrogen or a hydroxy protecting group,  
in an inert solvent with a reducing agent or with a reducing agent in the presence of a  
chiral auxiliary,

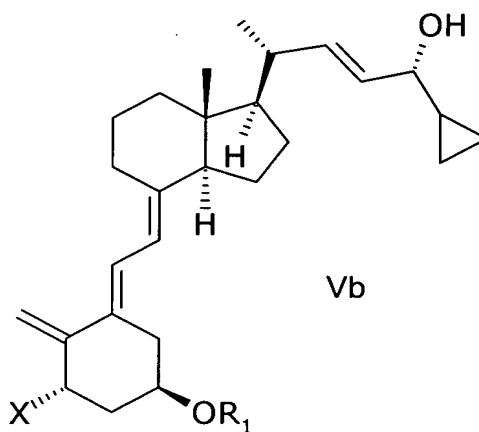
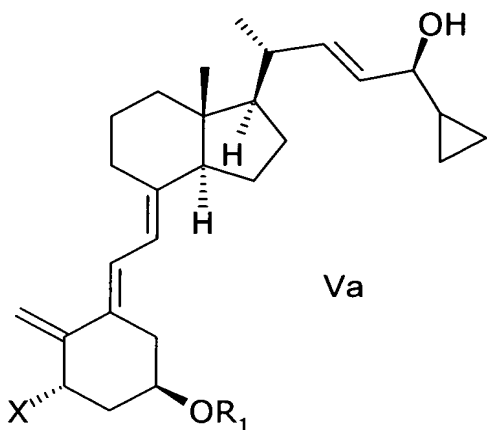
to give a mixture of compounds of general structure IVa and IVb,

5 which is enriched with IVa,



wherein X and  $R_1$  are as defined above;

(k) reacting the mixture of compounds of general structure IVa and IVb, which is  
enriched with IVa, in the presence of a base to give a mixture of compounds of general  
10 structure Va and Vb, which is enriched with Va,

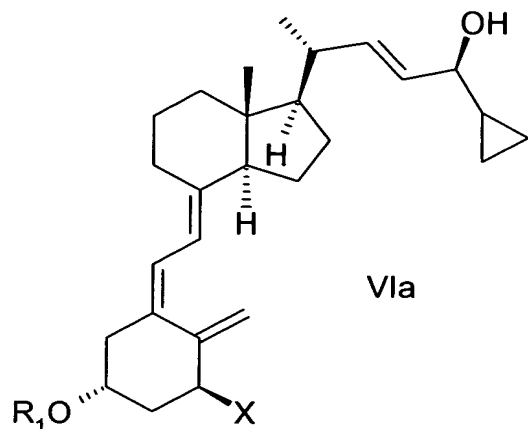


wherein X and  $R_1$  are as defined above;

(l) separating the compound of general structure Va from the mixture of compounds of  
general structure Va and Vb which is enriched with Va, wherein X and  $R_1$  are as defined  
15 above;

(m) hydroxylating the compound of general structure Va with a suitable hydroxylating  
agent, wherein X and  $R_1$  are as defined above to give a compound of general structure  
Va, wherein X represents  $OR_2$  and  $R_2$  represents hydrogen, and wherein  $R_1$  is as defined  
above;

(o) isomerising the compound of general structure Va to the compound of general structure VIa,

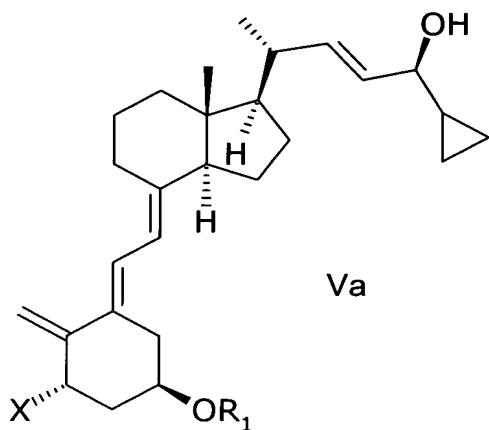


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wherein X, R<sub>1</sub> and R<sub>2</sub> are as defined above; and

(p) when R<sub>1</sub> is not hydrogen, removing the hydroxy protecting group R<sub>1</sub> of the compound of general structure VIa to generate calcipotriol or calcipotriol monohydrate.

- 10 5. A method for producing calcipotriol or calcipotriol monohydrate comprising steps (j) – (l) of claim 4 and further comprising the steps of:
- (q) protecting the C-24 hydroxy group of the compound of general structure Va,

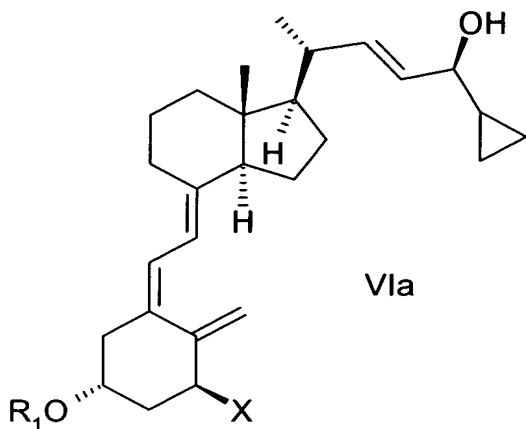


- 15 wherein X represents hydrogen, and wherein R<sub>1</sub> represents hydrogen or a hydroxy protecting group, with a hydroxy protecting group;
- (r) hydroxylating the C-24 hydroxy protected compound of general structure Va with a suitable hydroxylating agent, wherein X and R<sub>1</sub> are as defined above to give a C-24

hydroxy protected compound of general structure Va, wherein X represents OR<sub>2</sub> and R<sub>2</sub> represents hydrogen, and wherein R<sub>1</sub> is as defined above;

(s) removing the C-24 hydroxy protecting group of the compound of general structure Va;

- 5 (t) isomerising the compound of general structure Va to the compound of general structure VIa,



wherein X, R<sub>1</sub> and R<sub>2</sub> are as defined above; and

- 10 (u) when R<sub>1</sub> is not hydrogen, removing the hydroxy protecting group R<sub>1</sub> of the compound of general structure VIa to generate calcipotriol or calcipotriol monohydrate.

6. The method according to any one of claims 1-5, wherein the reducing step is in the presence of a chiral auxiliary.

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7. The method according to any one of claims 1-6, wherein the reducing agent is a borane derivative.

8. The method according to any one of claims 1-6, wherein the reducing agent is *N,N*-diethylaniline-borane, borane-tetrahydrofuran, or borane dimethylsulfide.

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9. The method according to any one of claims 1-8, wherein the chiral auxiliary is a chiral 1,2-amino-alcohol.

- 25 10. The method according to any one of claims 1-8, wherein the chiral auxiliary is a chiral *cis*-1-amino-2-indanol derivative.

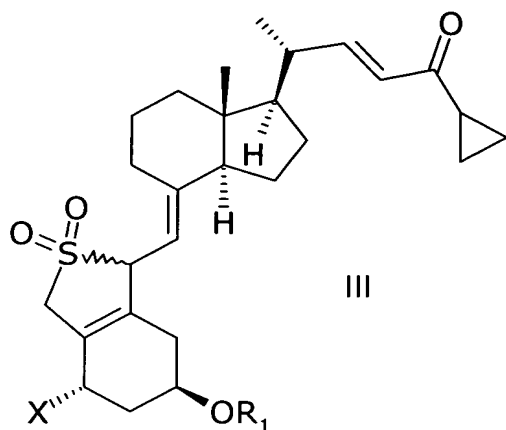
11. The method according to any one of claims 1-8, wherein the chiral auxiliary is (1*S*,2*R*)-(-)-*cis*-1-amino-2-indanol.

12. The method according to any one of claims 1-11, wherein the inert solvent is toluene, *tert*-butyl methyl ether, tetrahydrofuran, or mixtures thereof.

13. The method according to any one of claims 1-12, wherein the mixture of compounds of general structure IVa and IVb obtained by reducing a compound of general structure III has a molar ratio of IVa:IVb which is at least 56:44.

14. The method according to any one of claims 1-13, wherein the reducing step is carried out at a temperature between 10-20°C.

15. A method for producing a compound of general structure III,

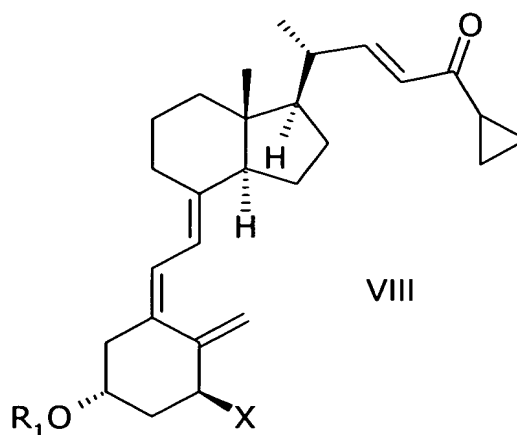
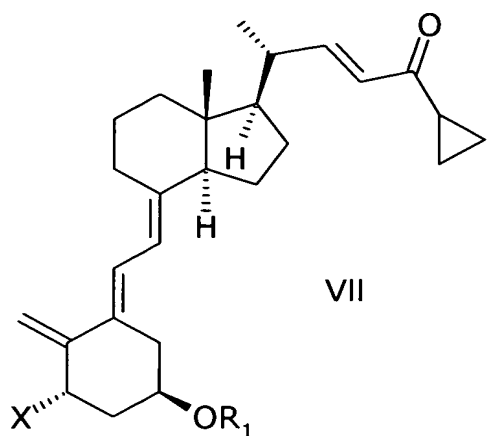


wherein X represents either hydrogen or OR<sub>2</sub>,

and wherein R<sub>1</sub> and R<sub>2</sub> may be the same or different and represent hydrogen, or a hydroxy protecting group,

by reacting a compound of general structure VII or VIII,

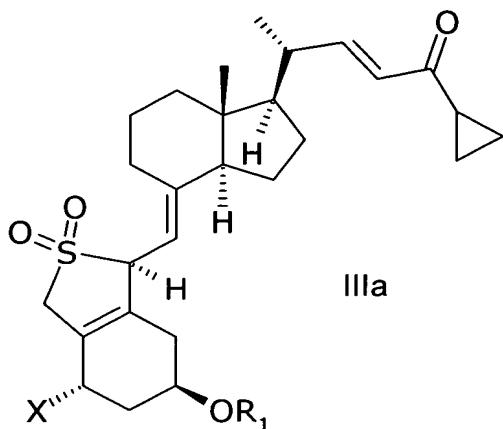




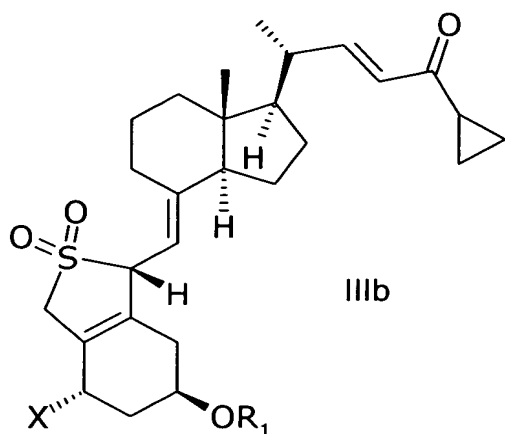
wherein  $R_1$  and  $R_2$  are as defined above,  
with sulphur dioxide.

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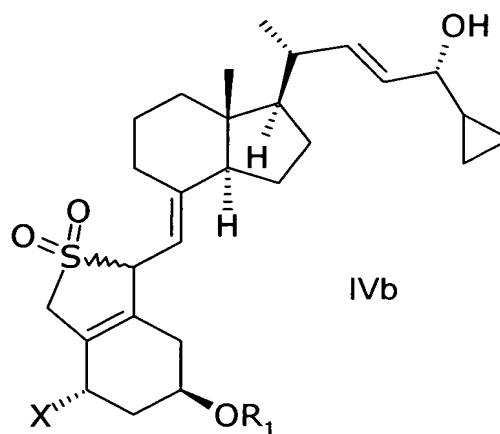
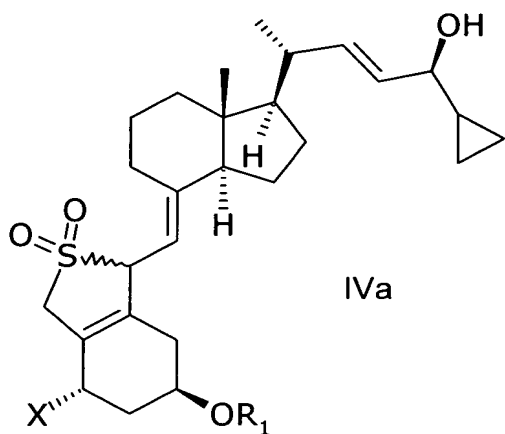
16. A method according to any one of claims 1-15, wherein the compound of general structure III is the epimer of general structure IIIa



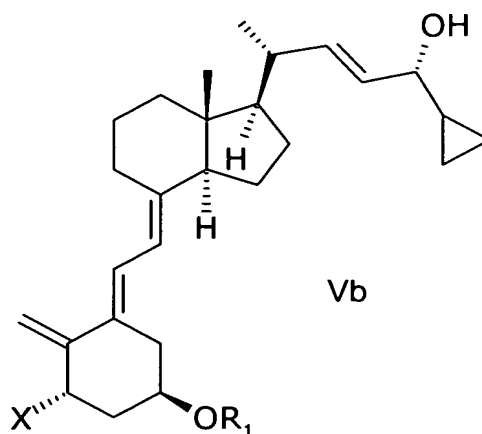
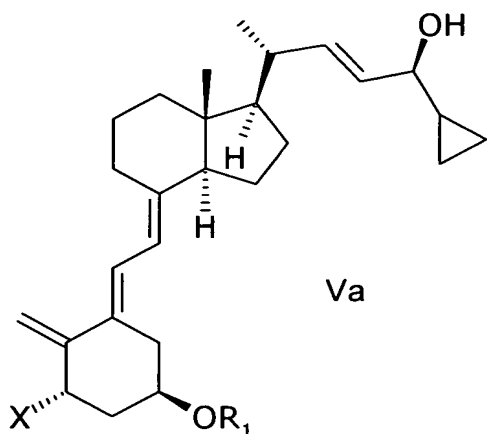
10 17. A method according to any one of claims 1-15, wherein the compound of general structure III is the epimer of general structure IIIb



18. A method of reacting the mixture of compounds of general structure IVa and IVb ,

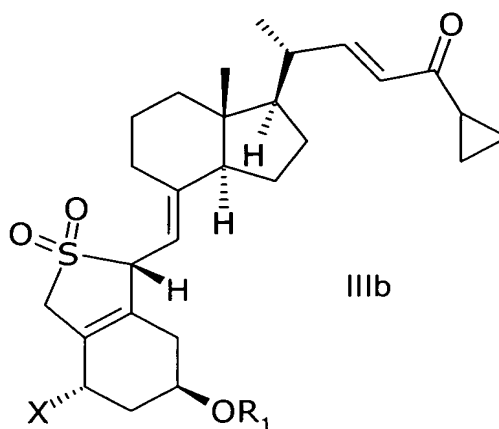
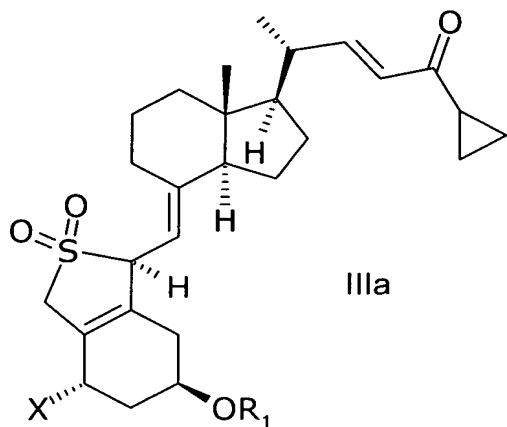


- 5 wherein X represents either hydrogen or  $OR_2$ ,  
 and wherein  $R_1$  and  $R_2$  may be the same or different and represent hydrogen, or a  
 hydroxy protecting group,  
 which is enriched with IVa, in the presence of a base to give a mixture of compounds of  
 general structure Va and Vb, which is enriched with Va,



wherein X, R<sub>1</sub>, and R<sub>2</sub> are as defined above.

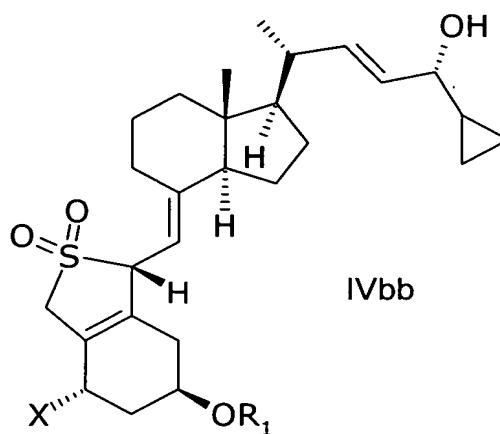
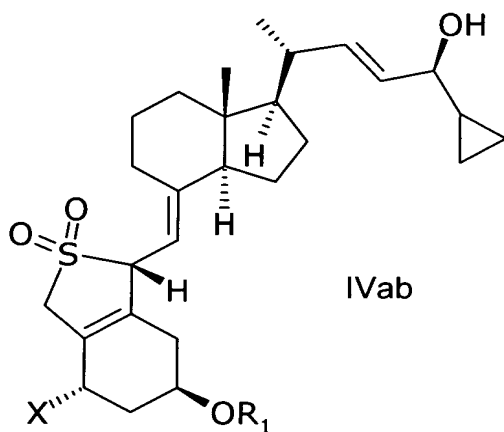
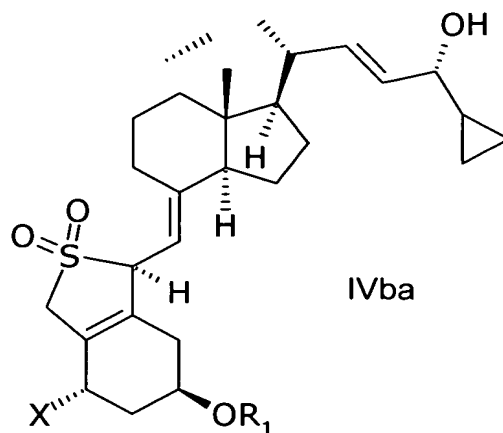
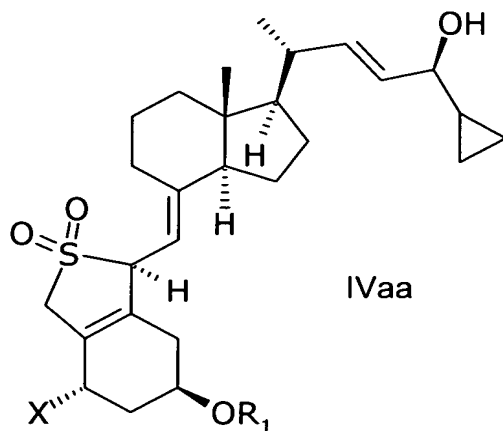
- 5 19. A method according to claims 1-3, 15, or 18, wherein X represents OR<sub>2</sub>.
20. A method according to any one of claims 1-19, wherein R<sub>1</sub> and/or R<sub>2</sub> represent alkylsilyl.
- 10 21. A method according to claim 20, wherein R<sub>1</sub> and/or R<sub>2</sub> represent *tert*-butyldimethylsilyl.
22. A method for producing calcipotriol {(5Z, 7E, 22E, 24S)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1 $\alpha$ -3 $\beta$ -24-triol} or calcipotriol monohydrate
- 15 comprising the method of any one of claims 1-21.
23. A compound of general structure IIIa or IIIb, or mixtures thereof,



wherein X represents either hydrogen or OR<sub>2</sub>,

and wherein  $R_1$  and  $R_2$  may be the same or different and represent hydrogen, or a hydroxy protecting group.

24. A compound of general structure IVaa, IVab, IVba, IVbb, IVb, or mixtures thereof,



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wherein  $\text{X}$  represents either hydrogen or  $\text{OR}_2$ ,

and wherein  $R_1$  and  $R_2$  may be the same or different and represent hydrogen, or a hydroxy protecting group.

10 25. A compound according to claim 23 or 24, wherein  $\text{X}$  represents  $\text{OR}_2$ .

26. A compound according to any one of claims 23-25, wherein  $R_1$  and  $R_2$  represent alkylsilyl.

15 27. A compound according to claim 26, wherein  $R_1$  and  $R_2$  represent *tert*-butyldimethylsilyl.

28. A compound according to any one of claims 23-25, wherein  $R_1$  and  $R_2$  represent hydrogen.

29. Use of a compound according to any one of claims 23-28 as an intermediate in the manufacture of calcipotriol or calcipotriol monohydrate.

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